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Original Article

Early neurological improvement after intravenous tissue plasminogen activator infusion in patients with ischemic stroke aged 80 years or older

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Abstract

Background: Early neurological improvement has been observed in patients with stroke receiving treatment with standard intravenous recombinant tissue plasminogen activator. However, the effectiveness of thrombolytic treatment and the risk of hemorrhagic transformation are not well understood in patients aged ≥80 years. In this study, we investigated the influence of age on early neurological improvement and hemorrhagic transformation rates in patients with stroke aged ≥80 years and receiving recombinant tissue plasminogen activator.
Methods: The study included 157 patients who received recombinant tissue plasminogen activator infusion at a teaching hospital. The National Institutes of Health Stroke Scale was used to evaluate stroke severity. Early neurological improvement was defined as an improvement of 8 or more points on this scale (compared with baseline) 24 hours after thrombolytic treatment. Neurological improvement was defined as an improvement of 8 or more points (compared with baseline) at discharge. Neurological deterioration was defined as an increase of 4 or more points (compared with baseline). Multivariate analysis was used to evaluate the associations among age, neurological improvement, and hemorrhagic transformation.
Results: The rate of early neurological improvement was 36.9% (58/157 patients) and the rate of hemorrhagic transformation was 22.3% (35/157 patients). At discharge, the rate of neurological improvement was 50.9% (80/157 patients) and the rate of neurological deterioration was 13.4% (21/157 patients). There was no statistically significant difference between patients aged ≥80 years and those <80 years of age with respect to rates of early neurological improvement, neurological deterioration, or hemorrhagic transformation. Among patients ≥80 years, the rate of neurological improvement in those receiving thrombolytic treatment was higher than the rate in those patients not receiving thrombolytic treatment (58.8% vs. 14.1%, $p < 0.01$). We concluded that thrombolysis increases the rate of neurological improvement in patients aged ≥80 years.
Conclusion: In older patients, thrombolytic treatment increased the rate of neurological improvement compared with patients not receiving the treatment. The study showed that thrombolytic treatment may be beneficial for patients ≥80 years, but should be performed with extreme care.

Keywords: cardioembolism; hemorrhagic transformation; ischemic stroke; outcomes; thrombolytic treatment

1. Introduction

In patients with acute ischemic stroke, intravenous thrombolysis using recombinant tissue plasminogen activator (rt-Pa) is associated with early recanalization and a better outcome.[1] In these patients, the goal of thrombolysis is to restore blood flow in the occluded artery to prevent brain tissue damage during reperfusion. Early neurological improvement (ENI) is defined as an improvement in the National Institutes of Health Stroke Scale (NIHSS) score of 8 or more points, or NIHSS scores equal to 0 or 1 at 24 hours following rt-Pa infusion. One study found that a higher ENI rate was observed in an rt-Pa group than in a control group.[2] The ENI rate is thought to be related to the restoration of blood flow in the occluded

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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artery.[3,4] As the thrombolytic effect of rt-Pa lasts for only 3.5 hours,[5] the response to thrombolysis is best evaluated after the first 24 hours. Among female patients, blood glucose levels of <8 mmol/L and the absence of cortical involvement are associated with major neurological improvement and good outcome at 3 months.[6] Previous studies have reported that intravenous infusion of rt-Pa in patients with stroke aged ≥80 years is associated with a lower probability of favorable outcome, a higher mortality, and an increased rate of hemorrhage.[7–9] However, other studies have shown that thrombolysis induced by rt-Pa in patients with stroke aged ≥80 years is both safe and beneficial.[10,11] A report on the intravenous infusion of rt-Pa in patients with stroke and cardiac myxoma showed that higher hemorrhagic transformation (HT) and lower response rates are observed in older patients.[12] Therefore whether or not the neurological response and HT rates are related to age remain a matter of contention. This study was conducted to investigate the influence of age on the rates of ENI and hemorrhage.

2. Methods

Our data were drawn from the stroke registry database of a teaching hospital in central Taiwan. We have regularly used rt-Pa in patients with acute stroke since January 2007. The data from all patients with stroke who received intravenous rt-Pa treatment between January 2007 and December 2012 were included in the study. All inclusion and exclusion criteria for thrombolytic treatment were based on the guidelines for stroke treatment in Taiwan, which state that patients ≥80 years of age should not be given thrombolytic treatment.[13] However, such patients aged ≥80 years without other contraindications, who arrived within 3 hours of the onset of stroke and requested thrombolytic treatment, were given rt-Pa infusion. The group not receiving rt-Pa included patients ≥80 years old who arrived at our hospital within 3 hours of stroke onset without contraindications for thrombolytic treatment other than old age, but who did not receive the treatment. Patients were followed-up using computed tomography (CT) or magnetic resonance imaging (MRI) of the brain 24 hours after rt-Pa infusion.

The NIHSS scale was used to assess stroke severity. An NIHSS-certified stroke team member at our facility performed the scoring and evaluation after every 6 hours for the first 24 hours, and at discharge. ENI was defined as an improvement of ≥8 points (compared with baseline) 24 hours after thrombolytic treatment, or an improvement in the NIHSS score of 0 or 1 towards the end of rt-Pa infusion. Neurological improvement (NI) was defined as ≥8 point improvement (compared with baseline) or an improvement in NIHSS score of 0 or 1 at discharge.[2] Neurological deterioration (ND) was defined as a ≥4 point increase in the NIHSS score (compared with baseline) at discharge.[10] Early ND was defined as a ≥4 point increase in the NIHSS score (compared with baseline) within 24 hours of rt-Pa infusion. HT was defined as any sign of hemorrhage on the follow-up CT or MRI scans. Symptomatic HT (SHT) was defined as blood clots in the brain observed during follow-up CT or MRI scans, with an increase in the NIHSS score of 4 or more points.[14] The data used in the study were collected from the Chia -Yi Christian Hospital acute stroke registry. This registry has been approved by the ethics committee of the hospital.

Statistical significance between the age groups was analyzed using the Chi-square test or Fisher's exact test for categorical variables and *t* test for continuous parameters, including NIHSS, blood pressure, and time from stroke onset to rt-Pa infusion (rt-Pa time). Logistic regression analysis was used to investigate the risk factors of HT and ENI. MedCalc for Windows, version 12.3 (MedCalc Software, Ostend, Belgium) was used for data analyses.

3. Results

From January 2007 to December 2012 in our hospital, 157 patients received intravenous rt-Pa for acute ischemic stroke within 3 hours of stroke onset. Follow-up by MRI was performed in 45.6% of these patients. During the 6-year study inclusion period, 78 patients presented to our hospital within 3 hours of stroke onset and were considered eligible for thrombolytic treatment (without contraindications for thrombolysis other than old age), but did not receive the treatment because of their age (≥80 years). Follow-up by MRI was performed in 60.2% of these patients. Of the patients who received thrombolytic treatment, 140 were <80 years old (younger group) and 17 were aged ≥80 years (older group). Table 1 gives the baseline characteristics of the patients. The baseline stroke severity was higher in patients aged ≥80 years than in patients aged <80 years. The older age group patients showed a higher prevalence of hypertension, atrial fibrillation,

Table 1
Baseline characteristics of patients (n = 157).

Age (y)	*n*	Male sex	HTN	DM	Prior stroke	AF	Heart disease	SBP-pre (mmHg)	Median NIHSS score	Rt-Pa time (min)	Smoker
<80	140	87	103 (73.4)	51 (36.3)	19 (12.5)	50 (36.3)	67 (48.9)	155.7	14	113.8	57 (42.6)
≥80	17	8	15 (92.8)	3 (7.10)	3 (21.4)	12 (71.4)	14 (92.8)	156.3	22	112.8	6 (21.47)
p			0.24[a]	0.17[a]	0.71[a]	<0.01[a]	0.12[a]	0.20[b]	0.001[b]	0.15[b]	0.79[a]

Data are presented as *n* (%).
AF = atrial fibrillation; DM = diabetes mellitus; HTN = hypertension; NIHSS = National Institutes of Health Stroke Scale; Rt-Pa time = time from stroke onset to recombinant tissue plasminogen activator infusion; SBP-pre = systolic blood pressure prior to thrombolysis.
[a] Chi-square test or Fisher's exact test.
[b] *t* test.

and heart disease. The interval between stroke onset and rt-Pa infusion was not significantly different between the two groups.

Twenty-four hours after intravenous rt-Pa infusion, ENI was seen in 58/157 (36.9%) patients; this rate was not significantly different between patients aged ≥80 years [9/17 (52.9%)] and those aged <80 years [49/140 (35%)] ($p = 0.18$; Table 2). HT was seen in 35/157 (22.3%) patients; the HT rate was not significantly different between patients ≥80 years [5/17(29.4%)] and those aged <80 years [30/140 (21.4%)] ($p = 0.53$; Table 2). SHT was observed in 10/157 (6.4%) patients; SHT was not significantly different between patients aged ≥80 years [2/17(11.7%)] and those aged <80 years [8/140 (5.7%)] ($p = 0.29$; Table 2). The stroke subtypes in the 157 patients were as follows: 57 cardioembolism, 45 large vessel disease, 12 small vessel occlusion, and 43 of unknown origin.[15] Of the 35 patients with HT, 22 had cardiogenic cerebral embolism, six had large vessel disease, and seven had stroke of unknown origin. In comparison with large vessel disease, cardiogenic cerebral embolism increased the risk of HT with an odds ratio of 3.97 (Table 3). In four of the 35 patients with HT, the hemorrhage was located outside the main stroke area; among these four patients, three were aged between 74 years and 80 years and one was 91 years old. Of the four patients, two were of the cardioembolism stroke subtype and two of an unknown origin. Followup by MRI was performed in two of these four patients. However, there was no significant change in the rates of HT between patients in the younger and older age groups ($p = 0.53$). At discharge, the NI rate was 51.6% (81/157) in all patients and 58.8% (10/17) in patients aged ≥80 years. The early ND rate was 14.1% (22/157), which was not significantly different between the older and younger groups ($p > 0.99$). The ND rate at discharge was 19.7% (31/157) in all patients and 11.7% (2/17) in patients aged ≥80 years, which was not significantly different between the older and younger groups ($p = 0.52$). In patients aged ≥80 years who did not receive thrombolysis, the NI rate was 14.1% (11/78) and the ND rate was 12.8% (10/78). In patients aged ≥80 years, the NI rate was significantly higher in the thrombolytic group than in the nonthrombolytic group ($p < 0.01$; Table 4). There was no significant difference in the HT and SHT rates between the thrombolytic and nonthrombolytic groups (29.4% vs. 10.3%, $p = 0.09$; 11.7% vs. 3.84%, $p = 0.46$; Table 4).

Fourteen of the 157 patients died during hospitalization and the in-hospital mortality was 8.9%. However, none of these 14 patients was aged ≥80 years. Among these 14 patients, 11 had middle cerebral artery occlusion and three had basilar artery occlusion. Four of the 11 (36.4%) patients with middle cerebral artery occlusion showed HT.

Table 3
Stroke subtype and risk of hemorrhagic transformation ($n = 157$).

Stroke subtype	n	Hemorrhage	Odds ratio	95% CI	p
CE	58	22	3.97	1.44–10.90	0.007
LAA	45	6	1		
SVO	12	0	0.24	0.01–4.62	0.3
UE	42	7	1.30	0.39–4.24	0.7

CE = cardioembolism; CI = confidence interval; LAA = large vessel disease; SVO = small vessel occlusion; UE = undetermined etiology.

4. Discussion

As thrombolysis with rt-Pa improves outcome in patients after stroke, it has become a common practice in many clinics. However, some medical centers do not recommend rt-Pa for patients aged ≥80 years.[13] This study was designed to investigate whether age affects the rates of ENI and HT in patients treated with intravenous rt-Pa.

In this study, patients aged ≥80 years showed a higher prevalence of hypertension, cardiovascular disease, and atrial fibrillation compared with patients <80 years old. However, this did not affect the rates of response and HT. The ENI rates in 36.9% of patients observed in this study were close to those observed in an earlier study by Saposnik et al,[6] in which 28% of patients showed higher rates of ENI. Furthermore, the rates of ENI in our study are moderately higher than those reported by Felberg et al,[4] where 22% of patients showed early dramatic recovery. This difference may be because all patients in the study of Felberg et al[4] had middle cerebral artery occlusion.

Mishra et al[11] reported that elderly patients who underwent thrombolysis treatment showed a better stroke outcome at 90 days compared with patients without thrombolysis. However, in addition to thrombolysis, patient condition and quality of patient care could play a part in this 90-day outcome. By contrast, our study focused on ENI, which is only related to the effect of thrombolysis and not the quality of patient care after discharge. The results of our study indicate that rt-Pa treatment may increase the rate of NI in older patients with stroke.

Table 2
Comparison of patient conditions after thrombolytic treatment between patients aged <80 years or ≥80 years ($n = 157$).

Age (y)	n	Male sex	ENI	ICH	SHT	Early ND	NI	ND
<80	140	87	49 (35.0)	30 (21.4)	8 (5.7)	20 (14.2)	70 (50.0)	29 (20.7)
≥80	17	8	9 (52.9)	5 (29.4)	2 (11.7)	2 (11.7)	10 (58.8)	2 (11.7)
Total	157	95	58 (36.9)	35 (22.3)	10 (6.4)	22 (14.1)	80 (50.9)	31 (19.7)
p[a]			0.18	0.53	0.29	> 0.99	0.61	0.52

Data are presented as n (%).
ENI = early neurological improvement; early ND = neurological deterioration within 24 hours of rt-Pa infusion; ICH = intracranial hemorrhage; ND = neurological deterioration at discharge; NI = neurological improvement at discharge; SHT = symptomatic hemorrhagic transformation.
[a] Chi-square or Fisher's exact test, where appropriate.

Table 4
Comparison of baseline characteristics between treatment and non-treatment with recombinant tissue plasminogen activator in patients aged ≥80 years ($n = 95$).

Rt-pa	*n*	Median NIHSS score	DM	HTN	Prior stroke	AF	NI	ND	HT	SHT
Yes	17	17.5	2 (11.2)	16 (94.1)	4 (23.5)	12 (70.5)	10 (58.8)	3 (17.6)	5 (29.4)	2 (11.7)
No	78	13	16 (20.5)	66 (84.6)	22 (28.2)	32 (44.1)	11 (14.1)	10 (12.8)	11 (10.3)	3 (3.84)
p		0.62[b]	0.62[a]	0.51[a]	0.92[a]	0.05[a]	0.007[a]	0.69[a]	0.09[a]	0.46[a]

Data are presented as *n* (%).
AF = atrial fibrillation; DM = diabetes mellitus; HT = hemorrhagic transformation; HTN = hypertension; ND = neurological deterioration; NI = neurological improvement; NIHSS = National Institutes of Health Stroke Scale; SHT = symptomatic hemorrhagic transformation.
[a] Chi-square or Fisher's exact test, where appropriate.
[b] *t* test.

Our study showed that, in comparison with patients <80 years, patients aged ≥80 years did not have an increased risk of SHT or HT after thrombolytic treatment. In addition, there was no significant difference in the rate of ENI or NI in patients receiving thrombolytic treatment. However, in older patients, thrombolytic treatment did not increase the risk of HT or SHT compared with that of patients not receiving thrombolytic treatment. Furthermore, in our study we noticed higher HT rates among patients aged 50–59 years and ≥80 years. Moreover, because most HT occurred in patients with total anterior circulation infarctions, we propose that the hemorrhagic rate is not influenced by age, but primarily depends on the type of stroke. After thrombolysis, four patients aged >74 years developed brain hemorrhage outside the main area of the infarct. This may be due to small cardioembolism or microaneurysm, which was undiagnosed in CT scans of the brain.[16]

Patients with stroke and atrial fibrillation have a higher risk of mortality and intracerebral hemorrhage.[17] In our study, the cerebral hemorrhage rate among patients aged ≥80 years not receiving thrombolysis was 10.3%; this is higher than that reported by Frank et al,[18] and lower than that of Lee et al.[19] The study by Frank et al[18] reported intracranial hemorrhage in 2.7% of patients with stroke without atrial fibrillation, and 3% of patients with atrial fibrillation.[18] The study of Lee et al,[19] by contrast, reported intracerebral hemorrhage in 15% of patients.

HT after thrombolytic treatment occurred in 35(22.3%) patients. Of note, 10 (6.4%) patients displayed SHT. The HT and SHT rates were lower than those reported by Bang et al,[20] who found HT in 46.4% and SHT in 18.9% of patients who received intra-arterial thrombolysis. The lower HT rate observed in our study may be partly caused by the fact that only 6.8% (3/44) of the patients with atrial fibrillation regularly took anticoagulant drugs prior to their stroke.

Our study has certain limitations. Firstly, our data were based on regular clinical practice registration and not on randomized trials. Secondly, the guidelines in Taiwan for using rt-Pa in patients with stroke aged ≥80 years may have caused a selection bias. Thirdly, we did not perform routine follow-up cerebral imaging for the detection of hemorrhage in patients who were not treated by thrombolysis, which may have resulted in an underestimation of the hemorrhagic rate.

In conclusion, thrombolysis did not decrease the rates of ENI or HT in older patients with stroke compared with patients in other age groups. In older patients, thrombolysis may result in an increase in the NI rate compared with that in older patients not receiving thrombolysis. This study showed that thrombolysis in patients aged ≥80 years may have a beneficial outcome when performed with extreme care.

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